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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,074	02/16/2001	Gokhan S. Hotamisligil	21509-044	4331

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/788,074	Hotamisligil
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 30, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *16, 22-24, 27, and 31-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *16, 22-24, 27, and 31-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed June 30, 2003, Paper No. 15.

Claims 16, 22-24, 27 and 31-36 are pending in the instant application.

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 depends from a cancelled claim. It is unclear which pending claim it depends (or should depend) from. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

Claim 16, 22-24, 27 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of diagnosing a risk of developing insulin resistance in a mouse or human comprising determining the level of Mal1 transcript, wherein the transcript comprises at least 10 nucleotides of SEQ ID NO: 4 or its complement.

The art teaches extensive homology (40-60%) between Mal1 and other iLBP family members (see last paragraph on page 2894-first paragraph on page 2895 of Kane et al, reference "**CL**", submitted with IDS filed May 3, 2002, Paper No. 10). The specification and claims do not indicate which nucleotides (i.e. 10 nucleotides) of SEQ ID NOs: 4 or 2 are specifically representative of Mal1 transcript expression and do not share homology with other iLBP family members. The scope of the claims reads on numerous structural variants and specific, not general, guidance is needed to determine which minimum of 10 nucleotides of SEQ ID NOs: 4 or 2 specifically indicates and increase in Mal1 transcript. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus comprising a 10 nucleotide transcript (of SEQ ID Nos: 2 or 4) that specifically represents Mal1 transcript expression.

Claims 16, 22-24, 27, 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of diagnosing a risk of developing insulin resistance in a mouse or a human comprising determining the level of Mal1 transcript or polypeptide by at least 5%, wherein the increase in Mal1 transcript or polypeptide relative to a normal control tissue indicates a risk of developing insulin resistance.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention claimed.

The state of the prior art and the predictability or unpredictability of the art. Mal1 is a member of the multigene family of intracellular lipid-binding proteins (iLBP's), and Mal1 has been found to be overexpressed in neoplastic skin cells (see Kane et al generally, reference "**CL**", submitted with IDS filed May 3, 2002, Paper No. 10). Mal1 has been found to share significant sequence homology with other members of the iLBP family, including between 50-60% sequence identity with adipocyte iLBP and myelin P2 (see last paragraph on page 2894-first paragraph on page 2895 of Kane et al) and between 30-60% sequence similarity with other iLBP family members, including FABP and RAPB (first paragraph on page 2895 of Kane et al).

The instant specification discloses a correlation between genetic ablation of Mal1 in mice and decreases in body weight, reduction in circulating lipids and increased systemic insulin sensitivity (see especially page 5 of the instant specification).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of diagnosing a risk of developing insulin resistance in any organism comprising determining the level of Mal1 expression. The specification teaches a correlation between genetic ablation of Mal1 in mice and decreases in body weight, reduction in circulating lipids and increased systemic insulin sensitivity. One skilled in the art would not accept on its face the examples given in the specification of the observed decreases in body weight or circulating lipids, and increased systemic insulin sensitivity, as being correlative or representative of the successful diagnosis of a subject at risk of developing insulin resistance comprising a comparison of expression of Mal1. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with the ability to quantitate and compare expression of Mal1 transcripts or polypeptides in a normal human or mouse with one at risk of developing insulin resistance. Furthermore, the ability to assay differences in Mal1 transcript expression comprising measuring at least 10 nucleotides of said transcript involves an assay that specifically measures Mal1 transcript. Since the prior art teaches extensive sequence similarity between various iLBP family members, it would require undue experimentation to determine which transcript comprising 10 nucleotides would specifically

reflect an increase in Mal1 transcript expression, as opposed to an increase in other iLBP family members.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of diagnosing a risk of developing insulin resistance in a mouse or a human comprising determining the level of Mal1 transcript or polypeptide by at least 5%, wherein the increase in Mal1 transcript or polypeptide relative to a normal control tissue indicates a risk of developing insulin resistance. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of Mal1 transcript or polypeptide expression in normal subjects and those at risk of developing insulin resistance, whereby determination of transcript or polypeptide is reproducible and quantifiable, and further whereby a statistically significant difference is observed between normal subjects and those at risk. Since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

September 21, 2003

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER